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JACC STATE-OF-THE-ART REVIEW

Fibrinolytic Therapy for Thromboembolic Diseases

Approved Indications and Future Directions

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ABSTRACT

Fibrinolytic therapy plays a pivotal role in the management of thromboembolic diseases by promoting plasmin-mediated fibrin degradation and vessel recanalization, which frequently comes at the cost of increased risk of hemorrhagic events, including intracranial bleeding. Since the discovery of streptokinase in 1933, several additional fibrinolytic agents have been developed. Two plasminogen activators—urokinase and tissue plasminogen activator (tPA)—were identified in human samples. Through recombinant DNA technology, tPA was cloned and modified to produce alteplase. Subsequent efforts to prolong its plasma half-life led to the development of mutant derivatives such as tenecteplase and reteplase. Although fibrinolytic therapy in patients with ST-segment elevation myocardial infarction is currently restricted to those who cannot undergo primary percutaneous coronary intervention within 120 minutes of presentation, it has been a mainstay treatment for acute ischemic stroke and pulmonary embolism (PE) with hemodynamic compromise. Catheter-directed fibrinolysis has been evaluated in patients with intermediate-risk PE, deep vein thrombosis, acute limb ischemia, and after endovascular thrombectomy for ischemic stroke. Fibrinolytic agents have also been used in other clinically important indications, such as central venous access device thrombosis, mechanical prosthetic valve thrombosis, left ventricular assist device thrombosis, central retinal artery occlusion, cerebral venous sinus thrombosis, and left ventricular thrombus. This paper provides a comprehensive overview of the current applications, approved indications, evolving roles, and future directions of fibrinolytic agents in thromboembolic diseases.
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ABBREVIATIONS AND ACRONYMS

CVAD = central venous access device

CVST = cerebral venous sinus thrombosis

DVT = deep vein thrombosis

EMA = European Medicines Agency

FDA = United States Food and Drug Administration

LVAD = left ventricular assist device

MPVT = mechanical prosthetic valve thrombosis

PCI = percutaneous coronary intervention

PE = pulmonary embolism

STEMI = ST-segment elevation myocardial infarction

Fibrinolytic agents enhance the conversion of plasminogen into plasmin, resulting in the degradation of fibrin to recanalize occluded vessels.[1] Reestablishing blood flow can relieve ischemic symptoms, restore hemodynamic stability, and prevent adverse events.[1] However, fibrinolytic agents increase the risk of bleeding, including intracranial bleeding, caused by systemic plasmin activation and destabilization of hemostatic microthrombi that stabilize vascular injury.[1,2]

Since the discovery of streptokinase in 1933,[3] several other fibrinolytic agents have been developed. In humans, 2 plasminogen activators were detected: urokinase and tissue plasminogen activator (tPA).[1] Using recombinant DNA methods, tPA was cloned to produce alteplase.[4] Efforts to increase the plasma half-life of tPA led to the development of other fibrinolytic medications such as tenecteplase and reteplase.[2] In addition, several other agents—such as recombinant staphylokinase and prourokinase—were developed and are being evaluated in patients with various thromboembolic conditions.

Fibrinolytic drugs have been used to treat arterial and venous thromboembolic diseases. In patients with ST-segment elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PCI) is the preferred reperfusion strategy.[5,6] However, fibrinolytic therapy is an option for patients who cannot undergo primary PCI within 120 minutes of presentation if not contraindicated.[7] Systemic fibrinolysis has been a main treatment option for patients with pulmonary embolism (PE) presenting with hemodynamic compromise[8-10] but is underused because of concerns about intracranial hemorrhage.[11-13] Catheter-directed delivery of lower-dose fibrinolytic agents has also been studied in patients with PE and right ventricular (RV) dysfunction without hemodynamic instability[14,15] as well as those with proximal deep vein thrombosis (DVT).[16,17] Moreover, systemic fibrinolytic therapy is considered one of the cornerstones of acute ischemic stroke treatment,[18-20] and intra-arterial fibrinolysis has been examined as an adjunct to endovascular thrombectomy in patients with large vessel occlusion acute ischemic stroke.[21-27] In addition, fibrinolytic agents have been used for the management of acute limb ischemia,[28,29] central venous access device (CVAD) occlusion,[30-32] mechanical prosthetic valve thrombosis (MPVT),[33-35] left ventricular assist device (LVAD) occlusion,[36,37] cerebral venous sinus thrombosis (CVST), left ventricular (LV) thrombus, and central retinal artery occlusion (CRAO).[38,39] This review outlines the current role of fibrinolytic agents in thromboembolic diseases, summarizes the indications as per regulatory authorities and recommendations by professional society guidelines, and highlights high-quality evidence from contemporary randomized controlled trials (RCTs) and future perspectives.

METHODS

We reviewed the recent major professional society recommendations for using fibrinolytic therapy in patients with thromboembolic diseases. Moreover, we summarized the approved indications by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for using fibrinolytic agents for thromboembolic diseases. We reviewed recent trends in the use of fibrinolytic therapy in patients with thromboembolic diseases based on large investigations from the United States, Europe, and other countries of the world. We reviewed contemporary as well as pivotal RCTs used by the FDA and EMA (Supplemental Table 1). In case of insufficient evidence from RCTs (eg, for

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mechanical prosthetic valve thrombosis), we summarized the best available evidence from prospective controlled cohort studies or other observational investigations. To focus on recent advances, we mainly concentrated on investigations published after January 1, 2014. Ultimately, we described the ongoing RCTs and gaps in knowledge for fibrinolytic therapy in various thromboembolic diseases.

ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION

Fibrinolytic therapy has been investigated extensively for STEMI (formerly Q-wave myocardial infarction), following promising findings for coronary reperfusion in the 1950s and 1960s.[1] Ensuing RCTs, despite variations in enrollment criteria and some of the results, suggested that streptokinase and alteplase, compared with placebo, reduced mortality after acute myocardial infarction.[40-42] Later, accelerated alteplase infusion over 1.5 hours compared with streptokinase resulted in a 14% relative risk reduction (95% CI: 5.9%-21.3%) in mortality.[43] Subsequent RCTs demonstrated that 30-day mortality (7.47% vs 7.24%; OR: 1.03; 95% CI: 0.91-1.18) and hemorrhagic or nonhemorrhagic stroke (1.64% vs 1.79%, $P = 0.50$)[44] were comparable between reteplase and alteplase in trials that included patients within 6 hours of symptom onset. Furthermore, tenecteplase showed similar reperfusion,[45] mortality (6.18% vs 6.15%), and intracranial hemorrhage rates (0.93% vs 0.94%, $P = 1.00$) but lower noncerebral bleeding events (26.43% vs 28.95%, $P < 0.001$) compared with alteplase[46] in patients presenting within 6 to 12 hours from onset of symptoms (Supplemental Table 2). Consequently, the FDA and EMA approved alteplase, reteplase, and tenecteplase for use in patients with STEMI[1,47] (**Figure 1**).

However, over time, primary PCI has become the standard treatment for STEMI.[48] A landmark meta-analysis of 23 RCTs showed a lower risk for the composite of reinfarction, stroke, and death with primary PCI compared with fibrinolysis (8% vs 14%, $P < 0.001$) as well as a reduction in short-term death (7% vs 9%, $P = 0.002$), regardless of fibrinolytic agent type[5] (**Table 1**). As such, the use of fibrinolytic therapy for patients with STEMI has declined in the United States[49,50] as well as in many other high-income countries[51-57] (**Figure 2**, Supplemental Table 3). However, fibrinolytic therapy remains useful in low- and middle-income countries, primarily because of limited access to timely primary PCI.[58,59] Further studies revealed that the mortality reduction associated with primary PCI over systemic fibrinolysis no longer existed when PCI-related delays exceeded 120 minutes.[58,59] The latest American College of Cardiology (ACC)/ American Heart Association (AHA)[60,61] and European Society of Cardiology (ESC)[7] guidelines recommended fibrinolytic therapy for patients with STEMI who do not have contraindications to fibrinolysis and have an estimated delay of more than 120 minutes from first medical contact to PCI (**Figure 3**).

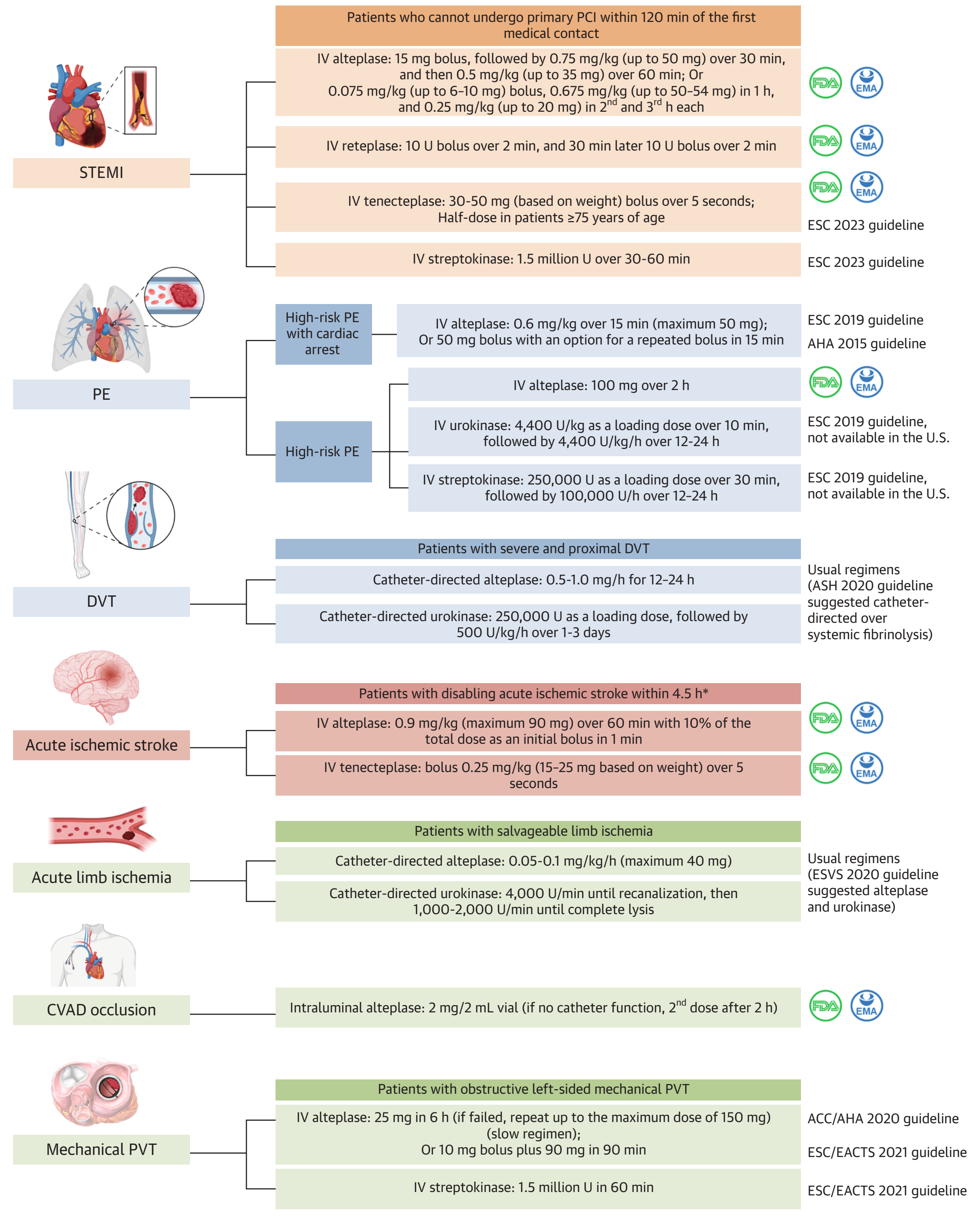
Recent RCTs have examined the effectiveness and safety of a pharmacoinvasive strategy involving fibrinolysis with tenecteplase followed by timely catheterization or rescue PCI if indicated, compared with primary PCI in patients within 3 hours of symptom onset who could not undergo primary PCI within 1 hour.[62,63] The results of the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial showed no significant differences between fibrinolytic therapy (followed by timely coronary angiography and PCI when indicated) and primary PCI for the composite outcome of 30-day death, shock, heart failure, or reinfarction (relative risk [RR]: 0.86; 95% CI: 0.68-1.09).[62] Intracranial bleeding occurred more frequently with fibrinolysis than primary PCI (1.0% vs 0.2%, $P = 0.04$).[62] The investigators reduced the tenecteplase dose by 50% in patients above 75 years of age after enrolling 21% of the target sample because of potential excess in intracranial hemorrhage, which lowered subsequent intracranial bleeding rates to 0.5%.[62] This dosing strategy has been incorporated in the most recent ESC guidelines.[6] Ongoing RCTs are evaluating the use of systemic recombinant staphylokinase (which is produced by recombinant DNA technology, is derived from Staphylococcus aureus, and is less immunogenic and more fibrin-specific than streptokinase[64]) for patients with STEMI (NCT05410925) and additional intracoronary fibrinolysis to PCI in those with high thrombus burden (NCT03998319 and NCT03335839) (Supplemental Table 4) adding to the existing evidence in this area.[65,66]

PULMONARY EMBOLISM

Several tools and markers are available for risk stratification of patients with PE. Briefly, those with systolic hypotension caused by PE are considered to have high-risk (massive) PE, whereas those with imaging or biomarker indices of RV dysfunction or injury are considered to have intermediate-risk (submassive) PE.[10]

Systemic fibrinolytic therapy for PE gained attention in the 1960s and 1970s.[67] Decades later, an RCT for hemodynamically unstable patients with PE

FIGURE 1 **Administration Protocol of Fibrinolytic Agents for Patients With Different Thromboembolic Diseases**



STEMI

Patients who cannot undergo primary PCI within 120 min of the first medical contact

- IV alteplase: 15 mg bolus, followed by 0.75 mg/kg (up to 50 mg) over 30 min, and then 0.5 mg/kg (up to 35 mg) over 60 min; Or 0.075 mg/kg (up to 6-10 mg) bolus, 0.675 mg/kg (up to 50-54 mg) in 1 h, and 0.25 mg/kg (up to 20 mg) in 2nd and 3rd h each — FDA EMA
- IV reteplase: 10 U bolus over 2 min, and 30 min later 10 U bolus over 2 min — FDA EMA
- IV tenecteplase: 30-50 mg (based on weight) bolus over 5 seconds; Half-dose in patients ≥75 years of age — FDA EMA; ESC 2023 guideline
- IV streptokinase: 1.5 million U over 30-60 min — ESC 2023 guideline

PE

High-risk PE with cardiac arrest

- IV alteplase: 0.6 mg/kg over 15 min (maximum 50 mg); Or 50 mg bolus with an option for a repeated bolus in 15 min — ESC 2019 guideline; AHA 2015 guideline

High-risk PE

- IV alteplase: 100 mg over 2 h — FDA EMA
- IV urokinase: 4,400 U/kg as a loading dose over 10 min, followed by 4,400 U/kg/h over 12-24 h — ESC 2019 guideline, not available in the U.S.
- IV streptokinase: 250,000 U as a loading dose over 30 min, followed by 100,000 U/h over 12-24 h — ESC 2019 guideline, not available in the U.S.

DVT

Patients with severe and proximal DVT

- Catheter-directed alteplase: 0.5-1.0 mg/h for 12-24 h
- Catheter-directed urokinase: 250,000 U as a loading dose, followed by 500 U/kg/h over 1-3 days

Usual regimens (ASH 2020 guideline suggested catheter-directed over systemic fibrinolysis)

Acute ischemic stroke

Patients with disabling acute ischemic stroke within 4.5 h*

- IV alteplase: 0.9 mg/kg (maximum 90 mg) over 60 min with 10% of the total dose as an initial bolus in 1 min — FDA EMA
- IV tenecteplase: bolus 0.25 mg/kg (15-25 mg based on weight) over 5 seconds — FDA EMA

Acute limb ischemia

Patients with salvageable limb ischemia

- Catheter-directed alteplase: 0.05-0.1 mg/kg/h (maximum 40 mg)
- Catheter-directed urokinase: 4,000 U/min until recanalization, then 1,000-2,000 U/min until complete lysis

Usual regimens (ESVS 2020 guideline suggested alteplase and urokinase)

CVAD occlusion

- Intraluminal alteplase: 2 mg/2 mL vial (if no catheter function, 2nd dose after 2 h) — FDA EMA

Mechanical PVT

Patients with obstructive left-sided mechanical PVT

- IV alteplase: 25 mg in 6 h (if failed, repeat up to the maximum dose of 150 mg) (slow regimen); Or 10 mg bolus plus 90 mg in 90 min — ACC/AHA 2020 guideline; ESC/EACTS 2021 guideline
- IV streptokinase: 1.5 million U in 60 min — ESC/EACTS 2021 guideline

Continued on the next page

terminated early after enrolling 8 patients, as all 4 patients randomized to heparin monotherapy died within 72 hours, whereas all 4 patients in the systemic streptokinase plus heparin group survived.[68] Pooled analyses in subsequent years shared more clarity about the tradeoffs of fibrinolysis in PE.[69-71] A study-level meta-analysis of 15 RCTs reported that systemic fibrinolysis was associated with a significant reduction in all-cause mortality compared with anticoagulation alone (OR: 0.59; 95% CI: 0.36-0.96) but with an increased risk of fatal or intracranial hemorrhage (OR: 3.18; 95% CI: 1.25-8.11)[69] (**Table 1**). Systemic administration of alteplase, streptokinase, and urokinase has been approved by both the FDA and EMA for the treatment of high-risk (hemodynamically unstable) PE.[1] Among these, only alteplase is currently available in the United States[1] (**Figure 1**). The guidelines recommend systemic fibrinolysis in patients with hemodynamic instability and advise against its routine use in stable patients[8,10,72,73] (**Figure 4**). However, epidemiologic data indicated that up to 70% of unstable patients who had no major contraindications for fibrinolysis still did not receive this treatment.[11-13] A recent RCT of 310 patients with high-risk PE showed that nonimmunogenic staphylokinase was noninferior to alteplase in reducing 7-day all-cause death (2% vs 3%; risk difference 0.6%; 95% CI: −2.8% to 4.0%, $P_{\text{noninferiority}}$ <0.001), with no major bleeding events with staphylokinase, compared with 3% in the alteplase group[74] (Supplemental Table 5).

For patients with intermediate to high-risk PE (ie, those without unstable hemodynamics but evidence of RV dysfunction and myocardial injury), the PEITHO (Fibrinolysis for Patients With Intermediate Risk Pulmonary Embolism) trial showed a significantly lower risk of death or hemodynamic deterioration with tenecteplase compared with placebo (2.6% vs 5.6%; OR: 0.44; 95% CI: 0.23-0.87).[75] However, the excess risk of major bleeding (11.5% vs 2.4%) and intracranial hemorrhage (5.1% vs 1.2%) resulted in the lack of adoption of this treatment.[75] Advancements in conventional and ultrasound-assisted catheter-directed fibrinolysis have provided alternative options for patients with intermediate-high-risk or high-risk PE with lower doses of fibrinolysis than systemic fibrinolysis, aiming to preserve efficacy while minimizing bleeding.[76] The FDA's clearance of ultrasound-assisted catheter-directed fibrinolysis for PE occurred in 2014, supported by the results of the ULTIMA (Ultrasound Accelerated Thrombolysis of Pulmonary Embolism)[14] and SEATTLE II(Ultrasound-Facilitated, Catheter-Directed Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism)[77] studies. The ULTIMA[14] RCT compared ultrasound-assisted catheter-directed fibrinolysis plus anticoagulation with anticoagulation alone in 59 patients with intermediate-risk PE and showed a mean decrease in RV to LV ratio from baseline to 24 hours of 0.30 ± 0.20 vs 0.03 ± 0.16 ($P < 0.001$), respectively, and no major bleeding events. The single-arm SEATTLE II[77] study showed a decrease in RV to LV diameter ratio from baseline to 48 hours postprocedure (1.55 vs 1.13, mean difference −0.42; $P < 0.001$), with 1 nonfatal major bleeding event (Supplemental Table 6). Subsequent RCTs, including SUNSET sPE (Standard vs Ultrasound-Assisted Catheter Thrombolysis for Submassive Pulmonary Embolism),[78] Kroupa et al,[79] and CANARY (Catheter-Directed Thrombolysis vs Anticoagulation in Patients With Acute Intermediate-High-Risk Pulmonary Embolism)[15] demonstrated that catheter-directed fibrinolysis may result in improved RV function and reduced pulmonary artery pressure without an increased risk of major bleeding compared with standard anticoagulation. Pooled estimates of trials have revealed low rates of major bleeding (1.8%; 95% CI: 0.2%-4.3%) and intracranial hemorrhage (0.4%; 95% CI: 0%-2.2%) following catheter-directed fibrinolysis in patients with intermediate-risk PE.[15]

FIGURE 1 Continued

Among fibrinolytic agents, only alteplase, reteplase, and tenecteplase have received FDA approval for at least 1 indication and remain available for clinical use in the United States.[1] Streptokinase and urokinase, although previously approved by the FDA, are no longer marketed in the United States.[1] Other agents, including recombinant staphylokinase and prourokinase, have not yet obtained FDA approval for any clinical indication and are not available for therapeutic use in the United States.[1] *The FDA has approved intravenous alteplase and tenecteplase for acute ischemic stroke within 3 hours of symptom onset.[120] The 3- to 4.5-hour window is supported by clinical guidelines[19,20] and approved by the EMA for both agents[121] but is not included in the FDA labeling.[120] ACC = American College of Cardiology; AHA = American Heart Association; ASH = American Society of Hematology; CVAD = central venous access device; DVT = deep vein thrombosis; EACTS = European Association for Cardio-Thoracic Surgery; EMA = European Medicines Agency; ESC = European Society of Cardiology; ESVS = European Society for Vascular Surgery; FDA = United States Food and Drug Administration; IV = intravenous; PCI = percutaneous coronary intervention; PE = pulmonary embolism; PVT = prosthetic valve thrombosis; STEMI = ST-segment elevation myocardial infarction. References: ESC 2023[6] for STEMI, ESC 2019[10] and AHA 2015[196] for PE, ASH 2020[8] for DVT, ESVS 2020[145] for acute limb ischemia, ACC/AHA 2020[197] and ESC/EACTS 2021[152] for mechanical prosthetic valve thrombosis.

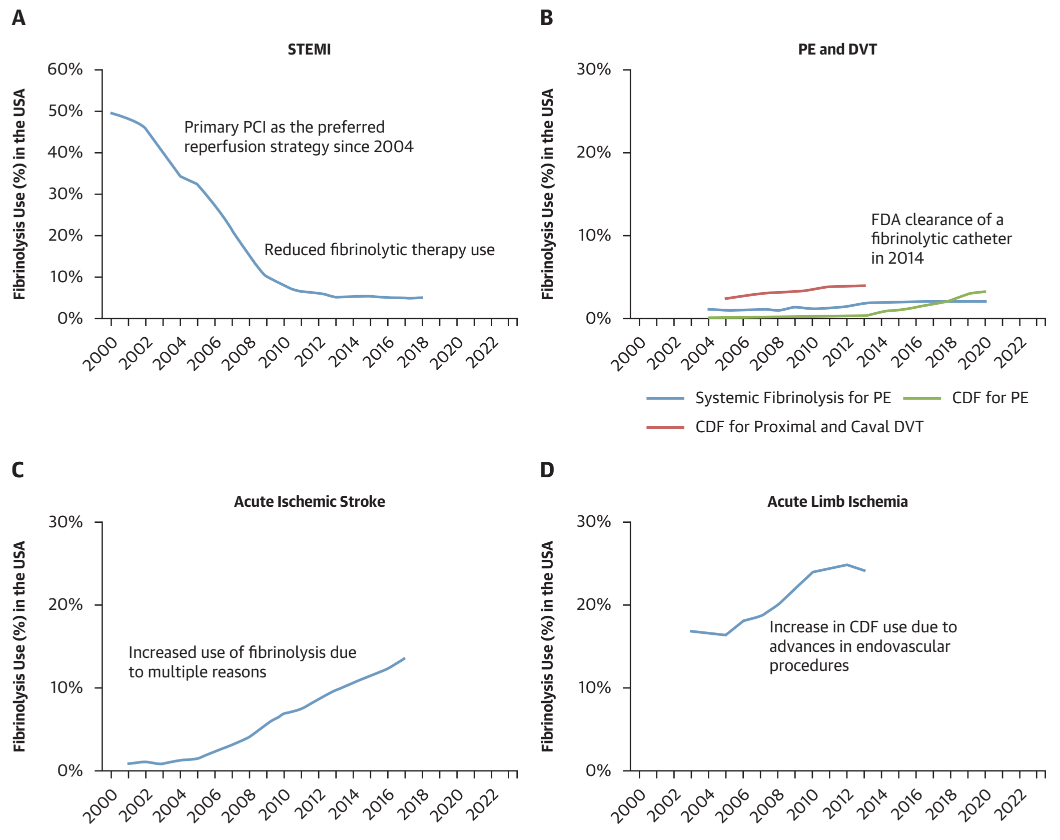
TABLE 1 Selected Systematic Reviews and Meta-Analyses of Randomized Trials for Fibrinolytic Therapy in Thromboembolic Diseases[a]

Study	Patient Population	Treatment vs Comparator	Number of RCTs/ Sample Size	Findings
STEMI				
Fazel et al, 2020[206,b]	Patients with STEMI	Primary PCI vs systemic fibrinolysis	31 RCTs with 15,357 patients	All-cause death (OR: 0.73; 95% CI: 0.61-0.89) Reinfarction (OR: 0.38; 95% CI: 0.29-0.50) Stroke (OR: 0.38; 95% CI: 0.24-0.60) Major bleeding (OR: 1.03; 95% CI: 0.72-1.49).
Jinatongthai et al., 2017[47,b]	Patients with STEMI	Systemic fibrinolysis (streptokinase, tenecteplase, or reteplase plus parenteral anticoagulation) vs Accelerated alteplase plus parenteral anticoagulation	40 RCTs with 128,071 patients	All-cause mortality: - Tenecteplase (RR: 1.01; 95% CI: 0.90-1.13) - Reteplase (RR: 1.04; 95% CI: 0.94-1.15) - Streptokinase (RR: 1.14; 95% CI: 1.05-1.24) Major bleeding: - Tenecteplase (RR: 0.79; 95% CI: 0.63-1.00) Reteplase (RR: 0.88; 95% CI: 0.69-1.12) Streptokinase (RR: 0.92; 95% CI: 0.70-1.21)
PE				
Zuo et al, 2021[70]	High-risk and Intermediate-risk PE	Fibrinolysis plus heparin vs heparin alone or plus placebo	21 RCTs with 2,401 patients	All-cause death (OR: 0.58; 95% CI: 0.38-0.80) PE recurrence (OR: 0.54; 95% CI: 0.32-0.90) Major bleeding (OR: 2.84; 95% CI: 1.92-4.20)
DVT				
Ashrafi et al, 2021[92,b]	Patients with acute proximal and iliofemoral DVT	Catheter-directed fibrinolysis or ultrasound-assisted catheter-directed fibrinolysis vs anticoagulation alone	7 RCTs with 1,047 patients	Post-thrombotic syndrome: Catheter-directed fibrinolysis (OR: 0.70; 95% CI: 0.30-1.64) Ultrasound-assisted catheter-directed fibrinolysis (OR: 0.59; 95% CI: 0.19-1.79) Bleeding events: Catheter-directed fibrinolysis (OR: 9.09; 95% CI: 0.42-195.23) Ultrasound-assisted catheter-directed fibrinolysis (OR: 5.71; 95% CI: 0.46-69.89)
Acute ischemic stroke				
Palaiodimou et al, 2024[119]	Patients with acute ischemic stroke within 4.5 hours of symptom onset	IV tenecteplase (0.25 mg/kg) vs IV alteplase	11 RCTs with 3,788 patients	mRS 0-1 (RR: 1.05; 95% CI: 1.01-1.10) mRS 0-2 (RR: 1.03; 95% CI: 0.99-1.07) sICH (RR: 1.12; 95% CI: 0.83-1.53) All-cause death (RR: 0.97; 95% CI: 0.82-1.15)
Kaesmacher et al, 2024[207]	Patients with acute ischemic stroke, eligible for IV fibrinolysis and thrombectomy	IV fibrinolysis before endovascular thrombectomy vs endovascular thrombectomy alone	6 RCTs with 2,313 patients	Shift in mRS by time from symptom onset to treatment: At 1 hour (OR: 1.49; 95% CI: 1.13-1.96) At 2 hours (OR: 1.25; 95% CI: 1.04-1.49) At 3 hours (OR: 1.04; 95% CI: 0.88-1.23) At 4 hours (OR: 0.87; 95% CI: 0.68-1.13) sICH by time from symptom onset to treatment: At 1 hour (OR: 1.46; 95% CI: 0.68-3.11)At 2 hours (OR: 1.42; 95% CI: 0.83-2.40) At 3 hours (OR: 1.37; 95% CI: 0.88-2.15) At 4 hours (OR: 1.33; 95% CI: 0.74-2.39)
Gunkan et al, 2025[208]	Patients with ischemic stroke beyond 4.5 hours of symptom onset or last known well without mechanical thrombectomy, selected by advanced neuroimaging	IV fibrinolysis (tenecteplase 0.25 mg/kg or alteplase) vs control	8 RCTs with 1,742 patients	mRS 0-1 (OR: 1.43; 95% CI: 1.17-1.75) mRS 0-2 (OR: 1.36; 95% CI: 1.12-1.66) sICH (OR: 4.25; 95% CI: 1.67-10.84) All-cause death (OR: 1.28; 95% CI: 0.87-1.89)
Acute limb ischemia				
Darwood et al, 2018[143]	Patients with acute or acute-on-chronic limb ischemia	Catheter-directed fibrinolysis vs surgery	5 RCTs with 1,292 patients	Limb salvage (OR: 1.02; 95% CI: 0.41-2.55) 30-day all-cause death (OR: 0.59; 95% CI: 0.31-1.14) Major bleeding (OR: 3.22; 95% CI: 1.79-5.78)

[a] Because of the limited number of RCTs, other thromboembolic conditions were not added to this table. [b] Network meta-analysis.

DVT = deep vein thrombosis; IV = intravenous; mRS = modified Rankin Scale; PE = pulmonary embolism; RCT = randomized controlled trial; RR = risk ratio; sICH = symptomatic intracranial hemorrhage.

FIGURE 2 **Recent Trends in the Use of Fibrinolytic Therapy in the United States for STEMI, PE and DVT, Acute Ischemic Stroke, and Acute Limb Ischemia**



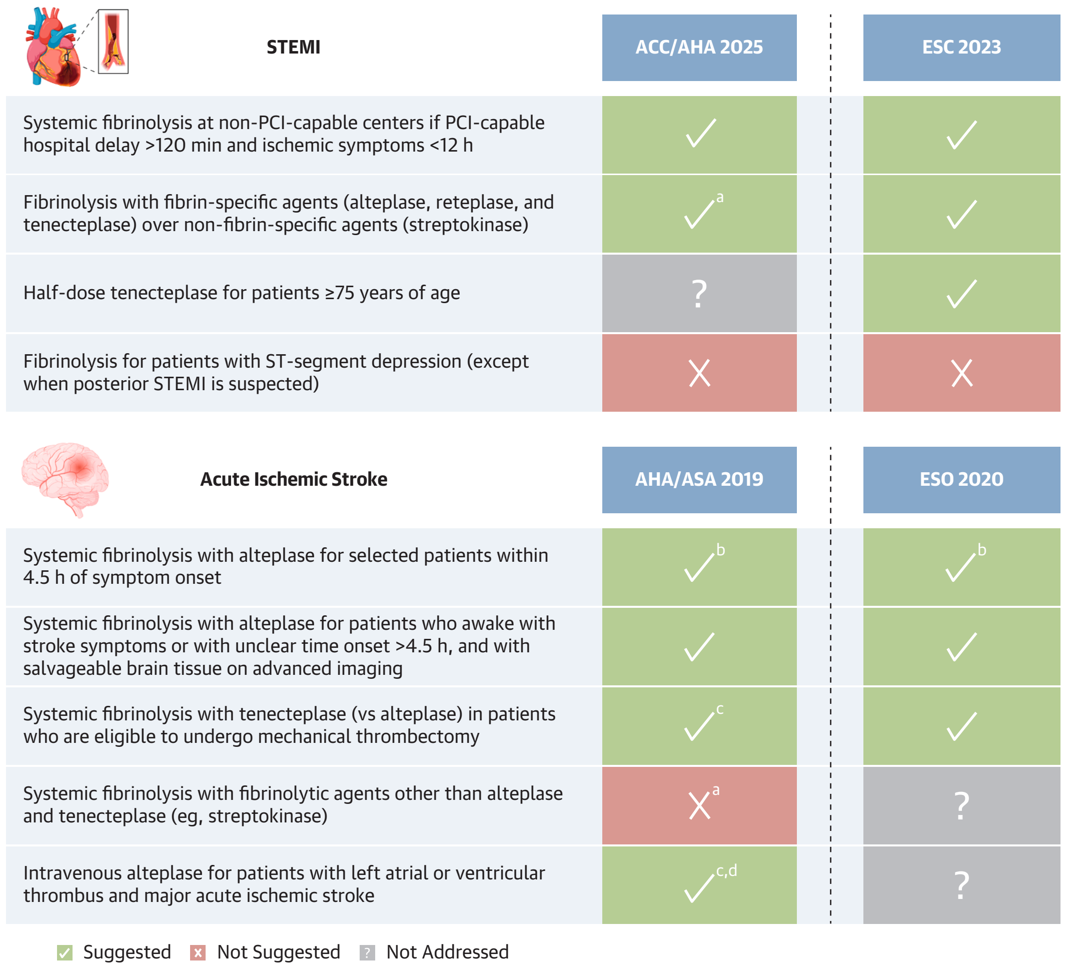
(A) The use of systemic fibrinolysis in patients with STEMI decreased during the past 2 decades in the United States following the availability of primary PCI.[49,50] For the first time, the ACC/AHA guideline for the management of patients with STEMI in 2004 recommended primary PCI as the preferred reperfusion strategy.[48] (B) The use of systemic and catheter-directed fibrinolysis in patients with PE has shown an increase in recent years.[198-201] Some reports showed an increase in the proportion of patients with lower extremity proximal and caval DVT treated with catheter-directed fibrinolysis between 2005 and 2013.[202] (C) In the past 2 decades, the rate of fibrinolytic therapy in patients with acute ischemic stroke has increased.[101,102] Several reasons may have contributed to this trend, as detailed in the text. (D) The use of catheter-directed fibrinolysis in acute limb ischemia increased from 2003 to 2013, probably because of the advances in endovascular procedures.[144] CDF = catheter-directed fibrinolysis; DRG = diagnosis-related group. Other abbreviations as in **Figure 1**.

Moreover, low-dose systemic fibrinolysis (≤50% of the standard dose of alteplase) plus anticoagulation, compared with anticoagulation alone, has been tested in an RCT of 121 patients with moderate PE (involving ≥2 lobar arteries or at least 1 of the main pulmonary arteries).[81] Compared with control, low-dose systemic fibrinolysis was associated with reduced rates of persistent pulmonary hypertension at 28 months (16% vs 57%, $P < 0.001$) and numerically reduced mortality (1.6% vs 5%, $P = 0.30$) and PE recurrence (0% vs 5%, $P = 0.08$) without any occurrence of bleeding events.[80]

The ongoing HI-PEITHO (Higher-Risk Pulmonary Embolism Thrombolysis)[81] and PE-TRACT (Pulmonary Embolism: Thrombus Removal With Catheter-Directed Therapy)[82] trials will help to define the efficacy of catheter-directed fibrinolysis in intermediate-risk PE. In parallel, the PEITHO-3[83] trial is testing the efficacy and safety of reduced-dose systemic fibrinolysis in this clinical setting (Supplemental Table 7).

Aside from fibrinolysis, mechanical thrombectomy options have also become available for patients with intermediate-risk or high-risk PE recently.[84] In the PEERLESS (Large-Bore Mechanical Thrombectomy vs Catheter-Directed Thrombolysis for Treatment of Intermediate-Risk Pulmonary Embolism) trial, among 550 randomized patients with intermediate-risk PE, no significant differences were observed in all-cause mortality (0.0% vs 0.4%, $P = 1.00$),

FIGURE 3 Key Recommendations From Major Professional Societies for Fibrinolytic Therapy in STEMI and Acute Ischemic Stroke



STEMI	ACC/AHA 2025	ESC 2023
Systemic fibrinolysis at non-PCI-capable centers if PCI-capable hospital delay >120 min and ischemic symptoms <12 h	✓	✓
Fibrinolysis with fibrin-specific agents (alteplase, reteplase, and tenecteplase) over non-fibrin-specific agents (streptokinase)	✓[a]	✓
Half-dose tenecteplase for patients ≥75 years of age	?	✓
Fibrinolysis for patients with ST-segment depression (except when posterior STEMI is suspected)	X	X

Acute Ischemic Stroke	AHA/ASA 2019	ESO 2020
Systemic fibrinolysis with alteplase for selected patients within 4.5 h of symptom onset	✓[b]	✓[b]
Systemic fibrinolysis with alteplase for patients who awake with stroke symptoms or with unclear time onset >4.5 h, and with salvageable brain tissue on advanced imaging	✓	✓
Systemic fibrinolysis with tenecteplase (vs alteplase) in patients who are eligible to undergo mechanical thrombectomy	✓[c]	✓
Systemic fibrinolysis with fibrinolytic agents other than alteplase and tenecteplase (eg, streptokinase)	X[a]	?
Intravenous alteplase for patients with left atrial or ventricular thrombus and major acute ischemic stroke	✓[c,d]	?

☑ Suggested ☒ Not Suggested ? Not Addressed

[a]Streptokinase is no longer available in the United States. [b]Not for mild nondisabling stroke. [c]Class of recommendation is IIb. [d]For patients presenting with moderate acute ischemic stroke likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV alteplase is of uncertain net benefit. ASA = American Stroke Association; CABG = coronary artery bypass grafting; MI = myocardial infarction; ESO = European Stroke Organization. Other abbreviations as in **Figure 1**. References: STEMI: ACC/AHA 2025[202]; ESC 2023.[6] Acute ischemic stroke: AHA/ASA 2019[20]; ESO 2020.[19]

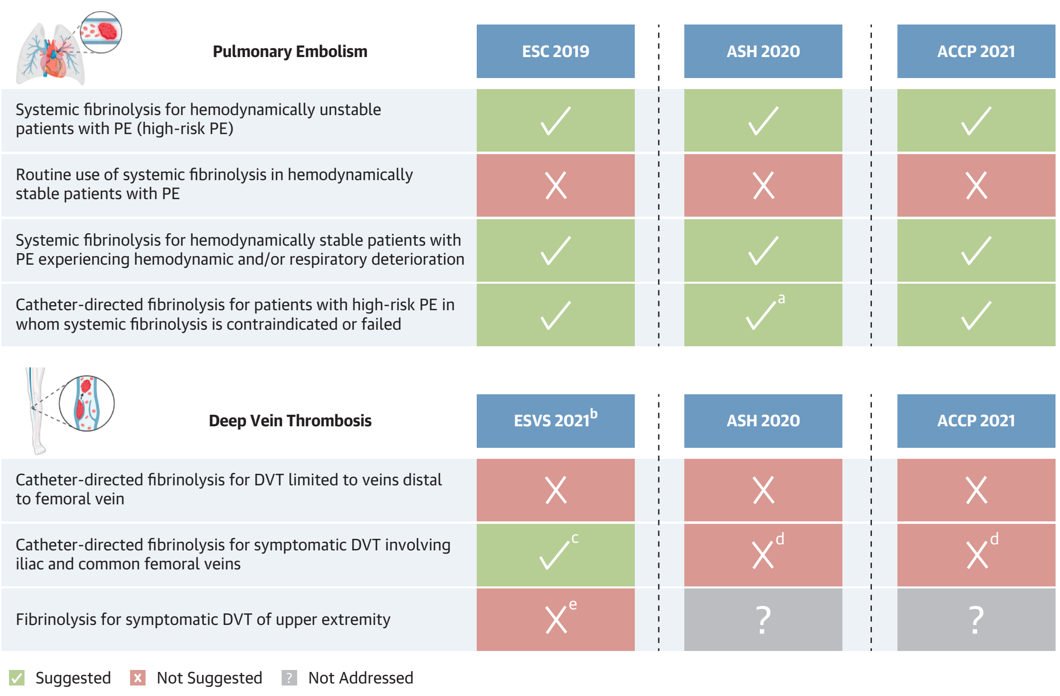
intracranial hemorrhage (0.7% vs 0.4%, $P = 0.62$), and major bleeding (6.9% vs 6.9%, $P = 1.00$) between large-bore mechanical thrombectomy and catheter-directed fibrinolysis, although the primary hierarchical composite outcome was in favor of mechanical thrombectomy, driven by fewer clinical deteriorations or bailouts and postprocedural intensive care unit admission and length of stay.[84]

DEEP VEIN THROMBOSIS

Fibrinolysis has been studied in DVT to reduce post-thrombotic syndrome (PTS), which presents as a constellation of dependent edema, chronic skin discoloration and change, pain, itching, and pressure sensation, and affects up to 50% of patients with DVT despite anticoagulation.[85,86] Despite improving venous patency (RR: 2.48; 95% CI: 1.35-4.57) and reducing the risk of PTS (RR: 0.54; 95% CI: 0.31-0.92),[87] systemic fibrinolysis, compared with anticoagulation monotherapy, increases the risk of major bleeding (RR: 2.45; 95% CI: 1.58-3.78)[87] and hence is not routinely considered for managing proximal DVT.[8,9]

RCTs of catheter-directed fibrinolysis in patients with proximal DVT have shown minimal benefits in

FIGURE 4 **Key Recommendations From Major Professional Societies for Fibrinolytic Therapy in PE and DVT**



Pulmonary Embolism	ESC 2019	ASH 2020	ACCP 2021
Systemic fibrinolysis for hemodynamically unstable patients with PE (high-risk PE)	✓	✓	✓
Routine use of systemic fibrinolysis in hemodynamically stable patients with PE	X	X	X
Systemic fibrinolysis for hemodynamically stable patients with PE experiencing hemodynamic and/or respiratory deterioration	✓	✓	✓
Catheter-directed fibrinolysis for patients with high-risk PE in whom systemic fibrinolysis is contraindicated or failed	✓	✓[a]	✓

Deep Vein Thrombosis	ESVS 2021[b]	ASH 2020	ACCP 2021
Catheter-directed fibrinolysis for DVT limited to veins distal to femoral vein	X	X	X
Catheter-directed fibrinolysis for symptomatic DVT involving iliac and common femoral veins	✓[c]	X[d]	X[d]
Fibrinolysis for symptomatic DVT of upper extremity	X[e]	?	?

✓ Suggested ☒ Not Suggested ? Not Addressed

[a]In centers with the appropriate infrastructure, clinical staff, and procedural experience. [b]Indications were provided for early thrombus removal in general, including surgical thrombectomy, catheter-directed fibrinolysis, and pharmacomechanical catheter-directed fibrinolysis. However, no specific recommendation was made regarding the preferred method of thrombus removal. [c]Class of recommendation IIa. [d]Except for patients with limb-threatening DVT or young patients with low bleeding risk. [e]Except for young and active patients with severe symptoms (within the first 2 weeks of symptom onset). ACCP = American College of Chest Physicians. Other abbreviations as in Figure 1. References: Pulmonary embolism: ESC 2019[10]; ASH 2020[8]; ACCP 2021.[74] Deep vein thrombosis: ESVS 2021[203]; ASH 2020[8]; ACCP 2021.[74]

preventing PTS, no significant improvement in quality of life, and no difference in the incidence of bleeding events when compared with anticoagulation alone.[17,88,89] However, the effect in patients with extensive DVT, including those with iliac or inferior vena cava extension of the thrombi, remains unknown. The CaVenT (Post-Thrombotic Syndrome After Catheter-Directed Thrombolysis for Deep Vein Thrombosis) trial[88] included 176 patients with first-time iliofemoral DVT, and catheter-directed fibrinolysis using alteplase was associated with a lower risk of PTS over 2 years (41.1% vs 55.6%, $P = 0.047$) compared with anticoagulation and compression therapy, although major bleeding events occurred only in the fibrinolysis group (3 vs 0). In a single-blind multicenter randomized trial with 184 patients,[89] ultrasound-accelerated catheter-directed fibrinolysis showed no PTS reduction at 12 months compared with standard care (anticoagulation, compression therapy, and early ambulation), although a significant reduction was observed at 36 months (OR: 0.40; 95% CI: 0.19-0.84). Only the treatment group experienced major bleeding events (5% vs 0%; OR: 9.25; 95% CI: 0.49-174.7). Furthermore, the ATTRACT (Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-Directed Thrombolysis) trial[17] found no significant reduction in PTS with pharmacomechanical fibrinolysis (catheter-directed fibrinolysis and mechanical thrombectomy) compared with anticoagulation alone (RR: 0.96; 95% CI: 0.82-1.11), and the intervention group experienced more major bleeding events (1.7% vs 0.3%, $P = 0.049$). A pooled analysis of seven RCTs,[90] including 1,217 patients, demonstrated a numerically lower incidence of PTS with catheter-directed fibrinolysis (OR: 0.70; 95% CI: 0.30-1.64) and ultrasound-assisted catheter-directed fibrinolysis (OR: 0.59; 95% CI: 0.19-1.79) compared with medical therapy; however, these differences were not statistically significant. Bleeding rates were numerically higher in ultrasound-assisted catheter-directed fibrinolysis (OR: 9.09; 95% CI: 0.42-195.23) and conventional catheter-directed fibrinolysis (OR: 5.71; 95% CI: 0.46-69.89) compared with medical therapy, although few events occurred and the differences did not reach statistical significance[90] (**Table 1**).

Overall, fibrinolytic therapy may be considered in selected high-risk patients, although systemic anticoagulation remains the first-line treatment, with recanalization procedures reserved for those with severe or persistent symptoms who have an extensive thrombus burden involving the common femoral or more proximal veins[8,9] (**Figure 4**).[91]

ACUTE ISCHEMIC STROKE

Fibrinolysis for acute ischemic stroke was mainly initiated following the 2 NINDS (National Institute of Neurological Disorders and Stroke) trials, which demonstrated that, compared with placebo, intravenous alteplase (0.9 mg/kg) administered within 3 hours of symptom onset led to improvement in favorable neurologic outcomes (39% vs 26%; OR: 1.7; 95% CI: 1.2-2.6) while increasing symptomatic intracerebral hemorrhage (6.4% vs 0.6%, $P < 0.001$).[18] These findings led to the FDA and EMA approval of alteplase for acute ischemic stroke treatment within the 0- to 3-hour window.[1] Subsequent RCTs of alteplase, including patients treated within 3 to 6 hours of symptom onset, did not show improvement in functional outcomes.[92-94] However, a pooled analysis of ECASS (European Cooperative Acute Stroke Study), ATLANTIS (Apixaban vs Standard of Care After Transcatheter Aortic Valve Implantation), and ECASS II suggested a modest but significant benefit in 3-month neurologic outcomes with alteplase administered within 3 to 4.5 hours of symptom onset (adjusted OR: 1.40; 95% CI: 1.05-1.85), although with a higher rate of intracerebral hemorrhage (5.9% vs 1.7%).[95] This pooled analysis, which offered greater statistical power than the individual trials to detect a significant benefit of intravenous fibrinolysis over placebo when administered within the 3- to 4.5-hour time window after onset of symptoms. Subsequently, the ECASS III trial, involving only patients 3 to 4.5 hours after acute ischemic stroke, also showed that excellent functional outcomes at 3 months occurred more frequently with alteplase compared with placebo (52.4% vs 45.2%; OR: 1.34; 95% CI: 1.02-1.76), at the cost of a greater incidence of symptomatic intracranial hemorrhage (2.4% vs 0.2%, $P = 0.008$).[96] In this context, the EMA extended the window for use of alteplase in ischemic stroke up to 4.5 hours, whereas the FDA maintained its original approval within the 0- to 3-hour window, noting the potential increased risk of hemorrhage beyond 3 hours[97] (**Figure 1**). The subsequent IST-3 (Third International Stroke Trial),[98] which included a broader range of patients (such as those aged >80 years who accounted for 53.3% of the study population), presented within 6 hours of symptom onset, did not confirm consistent benefit beyond 3 hours, including in patients treated at 3 to 4.5 hours. Enrollment in IST-3 followed the uncertainty principle, allowing inclusion only if both the clinician and the patient (or proxy) regarded the treatment as promising but unproven.[98] Although this broadened the study population, some concerns have been raised about potential selection bias caused by the exclusion of patients with a clear anticipated benefit or harm.[99]

The use of intravenous fibrinolysis for acute ischemic stroke has risen in the United States and Europe in the past 2 decades[100,101] (**Figure 2**). The establishment of primary stroke centers, campaigns such as AHA's Get With The Guidelines-Stroke quality improvement initiative;[102,103] improved hospital reimbursement for fibrinolysis;[104] and targeted improvements in emergency medical services, telemedicine, public education and stroke awareness campaigns, and mobile stroke units may have contributed to these trends.[105]

Beyond alteplase, several other fibrinolytic agents have been investigated for treating acute ischemic stroke. Tenecteplase, a modified form of alteplase with greater fibrin specificity and a longer half-life, allows for single bolus administration, simplifying delivery (even in an ambulance) compared with the continuous infusion required for alteplase.[1] Several RCTs have compared tenecteplase with alteplase.[106-118] A recent meta-analysis of 11 RCTs showed that, compared with alteplase, tenecteplase 0.25 mg/kg is associated with a significantly higher likelihood of excellent functional outcome (RR: 1.05; 95% CI: 1.01-1.10) and a similar probability of good functional outcome (RR: 1.03; 95% CI: 0.99-1.07) at 3 months[119] (**Table 1**). Comparable risks of symptomatic intracranial hemorrhage (RR: 1.12; 95% CI: 0.83-1.53) and 3-month mortality (RR: 0.97; 95% CI: 0.82-1.15) were noted for tenecteplase and alteplase.[119] The FDA has approved tenecteplase for the treatment of acute ischemic stroke within 3 hours of symptom onset,[120] whereas the EMA has approved its use within a 4.5-hour window.[121]

Several investigational fibrinolytic agents, including reteplase, recombinant staphylokinase, and recombinant prourokinase, have shown promising efficacy and safety compared with alteplase in acute ischemic stroke, with some trials suggesting improved functional outcomes or lower bleeding risk

(Supplemental Table 8). The RAISE (Reteplase vs Alteplase for Acute Ischaemic Stroke Within 4.5 Hours) trial showed that, compared with alteplase, reteplase (2 bolus doses of 18 mg) was associated with higher rates of 90-day excellent functional outcome (79.5% vs 70.4%; RR: 1.13; 95% CI: 1.05-1.21; $P = 0.002$ for superiority) without a significant difference in symptomatic intracranial hemorrhage (2.4% vs 2.0%; RR: 1.21; 95% CI: 0.54-2.75) in patients with ischemic stroke within 4.5 hours after onset of symptoms.[122] Recombinant nonimmunogenic staphylokinase[123] and recombinant prourokinase[124,125] (ie, genetically engineered form of prourokinase that is a precursor of urokinase) showed comparable efficacy with numerically lower incidence of symptomatic intracranial hemorrhage compared with alteplase (Supplemental Appendix).

Recent evidence suggests that intravenous fibrinolysis might benefit selected patients with acute ischemic stroke beyond the conventional 4.5-hour window if guided by advanced imaging, such as magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI)-fluid-attenuated inversion recovery (FLAIR).[106] The EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) trial showed improved functional outcomes at 3 months with alteplase vs placebo in patients treated 4.5 to 9 hours after onset of symptoms who had salvageable tissue on perfusion imaging (adjusted RR: 1.44; 95% CI: 1.01-2.06).[126] In the WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) trial, alteplase, compared with placebo, similarly improved excellent functional outcomes (adjusted OR: 1.61; 95% CI, 1.09-2.36) in patients with unwitnessed onset of stroke (within 24 hours of the last known well) using DWI-FLAIR mismatch to identify eligible patients.[127] These findings have led to updated AHA guidelines recommending alteplase in the extended time window for carefully selected patients[20] (**Figure 3**). Conversely, the TWIST (Tenecteplase in Wake-Up Ischaemic Stroke Trial), which evaluated tenecteplase (0.25 mg/kg) vs control using noncontrast computed tomography (rather than advanced perfusion neuroimaging methods) for ischemic stroke first noticed upon awakening from sleep, did not show significant improvement in functional outcomes (adjusted OR: 1.18; 95% CI: 0.88-1.58).[128]

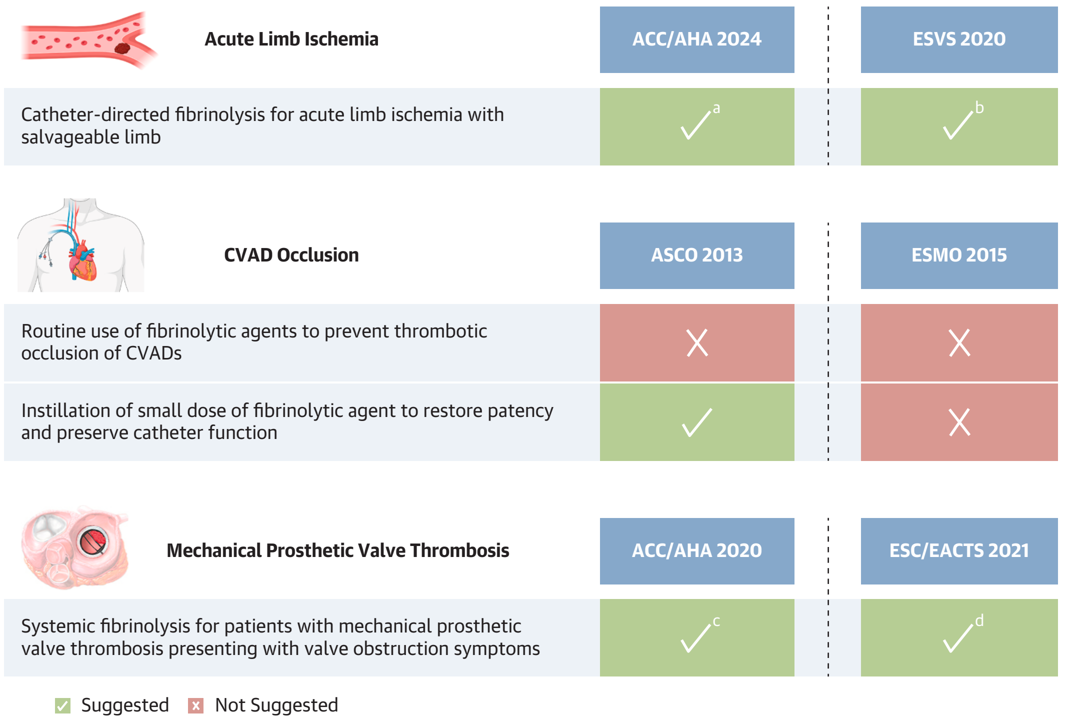
Systemic fibrinolysis has not been shown to provide clinical benefit in patients with minor, nondisabling ischemic stroke.[20] Multiple RCTs examining prourokinase,[129] tenecteplase,[130] and alteplase[131,132] against nonfibrinolytic comparators have failed to demonstrate improved functional outcomes over standard antithrombotic strategies. Routine fibrinolysis in this population may not improve clinical outcomes and can increase the risk of intracranial hemorrhage[129] (Supplemental Appendix).

Current guidelines continue to recommend administering intravenous fibrinolysis to eligible patients as quickly as possible, even when endovascular thrombectomy is being considered.[19,20] Moreover, intra-arterial fibrinolysis has been examined as an adjunct to endovascular thrombectomy in patients with large-vessel occlusion acute ischemic stroke to improve reperfusion outcomes.[21-27] Further details have been provided in the Supplemental Appendix regarding the completed and ongoing RCTs (Supplemental Table 9) and the potential role of fibrinolysis in addition to thrombectomy in patients with acute ischemic stroke[133,134] as well as the role of local fibrinolysis in patients with intraventricular hemorrhage to evacuate the hematoma and prevent hydrocephalus.[135-137]

ACUTE LIMB ISCHEMIA

Several RCTs compared catheter-directed fibrinolysis with surgical revascularization in patients with acute limb ischemia in the 1990s.[138-142] The STILE (Surgery vs Thrombolysis for Ischemia of the Lower Extremity) trial,[138] including 393 patients with acute limb ischemia, found that catheter-directed fibrinolysis vs surgery was associated with a higher rate for the composite outcome of death, major amputation, ongoing/recurrent ischemia, and major morbidity at 1 month (61.7% vs 36.1%, $P < 0.001$). The TOPAS (Thrombolysis or Peripheral Arterial Surgery) II trial,[139] enrolling 544 patients with acute limb ischemia, showed no significant differences in 6-month amputation-free survival between catheter-directed fibrinolysis and surgery (71.8% vs 74.8%, $P = 0.43$) but demonstrated increased risk of major bleeding with catheter-directed fibrinolysis (12.5% vs 5.5%, $P = 0.005$). A pooled analysis of these 5 RCTs showed no differences in limb salvage (OR: 1.02; 95% CI: 0.41-2.55), higher risk of major bleeding with fibrinolysis (OR: 3.22; 95% CI: 1.79-5.78), and numerically but not statistically significant lower 30-day mortality with fibrinolysis compared with surgery (OR: 0.59; 95% CI: 0.31-1.14).[143] The use of catheter-directed fibrinolysis has increased in the past decade for acute limb ischemia, potentially because of advances in catheter-directed techniques[144] (**Figure 2**). The 2024 ACC/AHA guideline for peripheral artery disease recommended catheter-directed fibrinolysis as the first-line therapy for patients with acute limb ischemia and salvageable

FIGURE 5 **Key Recommendations From Major Professional Societies for Fibrinolytic Therapy in Acute Limb Ischemia, CVAD Occlusion, and Mechanical Prosthetic Valve Thrombosis**



Acute Limb Ischemia	**ACC/AHA 2024**	**ESVS 2020**
Catheter-directed fibrinolysis for acute limb ischemia with salvageable limb	✓[a]	✓[b]
CVAD Occlusion	**ASCO 2013**	**ESMO 2015**
Routine use of fibrinolytic agents to prevent thrombotic occlusion of CVADs	✗	✗
Instillation of small dose of fibrinolytic agent to restore patency and preserve catheter function	✓	✗
Mechanical Prosthetic Valve Thrombosis	**ACC/AHA 2020**	**ESC/EACTS 2021**
Systemic fibrinolysis for patients with mechanical prosthetic valve thrombosis presenting with valve obstruction symptoms	✓[c]	✓[d]

☑ Suggested ☒ Not Suggested

[a]The indication for revascularization is described in general terms, encompassing both endovascular approaches (including catheter-directed fibrinolysis) and surgical interventions. [b]Indicated for Rutherford grade IIa. [c]Class I recommendation for ultra-slow regimen of fibrinolysis. [d]Class IIa recommendation for systemic fibrinolysis. ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; ESVS = European Society for Vascular Surgery. Other abbreviations as in **Figure 1**. References: Acute limb ischemia: ACC/AHA 2024[204]; ESVS 2020[145]; CVAD occlusion: ASCO 2013[31]; ESMO 2015[205]; mechanical prosthetic valve thrombosis: ACC/AHA 2020[197]; ESC/EACTS 2021.[152]

limbs[28] (**Figure 5**). Similarly, the 2020 European Society for Vascular Surgery guideline supported catheter-directed fibrinolysis in symptomatic patients with acute limb ischemia and salvageable limbs.[145] The more recent DUET (Dutch randomized Trial Comparing Standard Catheter-Directed Thrombolysis and Ultrasound-Accelerated Thrombolysis for Arterial Thromboembolic Infrainguinal Disease) trial compared standard catheter-directed fibrinolysis with ultrasound-accelerated catheter-directed fibrinolysis in 60 patients with acute limb ischemia.[146] Ultrasound-accelerated fibrinolysis was associated with reduced duration of fibrinolysis (17.7 ± 2.0 vs 29.5 ± 3.2 hours, $P = 0.009$) and urokinase dose (1.8 ± 1.0 vs 2.8 ± 1.6 million IU; $P = 0.01$) compared with standard catheter-directed fibrinolysis, whereas 30-day patency (82% vs 71%, $P = 0.35$) and a composite of death or severe adverse events (19% vs 29%, $P = 0.54$) were not significantly different between groups[146] (Supplemental Table 10). The ongoing FORAT (Thrombolysis With Recombinant Non-immunogenic Staphylokinase vs Surgery in Patients With Acute Limb Ischemia) trial (NCT05372718) will compare the effectiveness and safety of catheter-directed recombinant nonimmunogenic staphylokinase with surgery or endovascular interventions in 170 patients with acute limb ischemia (Supplemental Table 11). Ongoing advances in catheter-directed therapy underscore the need for safer and more effective fibrinolytic agents. Future trials should incorporate standardized, clinically meaningful outcomes to guide treatment strategies, including the use of novel agents for catheter-directed fibrinolysis in acute limb ischemia.

CENTRAL VENOUS ACCESS DEVICE OCCLUSION

CVAD occlusion remains a challenging problem for patients requiring durable vascular access. In a double-blind RCT of 50 thrombosed CVADs, a small intraluminal dose of alteplase (2 min/2 mL up to 2 doses), compared with urokinase, was associated with higher rates of complete function restoration (89.2% vs 59.1%, $P = 0.013$).[147] Alteplase received FDA approval for restoring CVAD function based on evidence from a phase 3 randomized, placebo-controlled trial[148] and a phase 3 open-label safety study[149] (**Figure 1**). In a combined analysis of these investigations involving 1,064 patients, catheter function was successfully restored in 85% of patients following up to 2 doses of alteplase without any intracranial hemorrhage or embolic events[150] and only 3 (0.3%) cases of major bleeding.[151] Tenecteplase[32] (2 min/2 mL up to 2 doses) and reteplase[150] (0.4 U up to 2 doses) have also been shown to restore catheter function in up to 87% and 94.7% of patients with occluded CVADs, although they have not received regulatory approval for this indication. The 2013 American Society of Clinical Oncology guideline recommended alteplase to restore the patency of nonfunctioning central venous catheters in patients with cancer[31] (**Figure 5**). However, the 2015 European Society for Medical Oncology guideline did not recommend fibrinolytic therapy as a first-line treatment because of concerns of thromboembolic risk.[30] This recommendation might be primarily based on theoretical concerns about dislodging thrombotic material following fibrinolysis. However, high-quality evidence demonstrating a frequent incidence of thromboembolic complications following fibrinolytic therapy for CVAD occlusion is limited.

MECHANICAL PROSTHETIC VALVE THROMBOSIS

The role of systemic fibrinolysis in treating recent MPVT is still debated.[152,153] Until a decade ago, evidence was limited to retrospective studies and their pooled analyses: a time when surgery was the preferred approach.[154] Since then, Özkan et al, in a series of prospective nonrandomized studies,[155,156] introduced the ultraslow low-dose fibrinolytic regimen (ie, 1 or several 25-hour/25-mg infusions of alteplase, with a maximal dose of 200 mg) and showed similar resolution of thrombosis and fewer major bleeding and thromboembolic events compared with higher and faster dose regimens. In a pilot RCT, Sadeghipour et al[35] compared ultraslow and fast regimens in patients with obstructive MPVT for complete fibrinolysis success (85.0% vs 78.3%; OR: 1.58; 95% CI: 0.25-1.63). Ischemic stroke ($n = 1$) and intracranial hemorrhage ($n = 3$) occurred only in those receiving the fast regimen. Although the ultraslow low-dose regimen has never been compared with surgery in an adequately powered clinical trial,[157] Özkan and colleagues[158] prospectively tested a stepwise algorithm for patients with obstructive MPVT in a nonrandomized study. Of 158 patients with MPVT suitable for surgery and fibrinolytic therapy, 83 were treated with fibrinolysis (bailout surgery in 4 patients), with a 90% thrombosis resolution rate.[158] Major bleeding (2.4% vs 9.3%), embolic complications (2.4% vs 5.3%), and rethrombosis requiring therapy (2.4% vs 6.7%) were less frequent in patients treated initially with fibrinolytic therapy than surgery.[158]

The lack of high-quality evidence has resulted in varying recommendations in the recent 2021 ESC/European Association for Cardio-Thoracic Surgery (EACTS) and 2020 ACC/AHA guidelines[152,153] (**Figure 5**). The ESC/EACTS guideline still recommends surgery as the main approach, remaining silent about the newly introduced ultraslow, low-dose fibrinolytic regimen.[152] On the other hand, the ACC/AHA guideline acknowledged the ultraslow, low-dose regimen and endorsed it as a class I recommendation for symptomatic patients with left-sided MPVT (especially those with moderate symptoms [NYHA functional class I-III] with thrombus size ≤ 0.8 cm^2).[153] Most recently, the SAFE-PVT (Surgery Compared to Fibrinolytic Therapy for Symptomatic Left-Sided Prosthetic Heart Valve Thrombosis) trial compared urgent surgery with the ultraslow, low-dose fibrinolytic regimen in 79 symptomatic patients with left-sided MPVT.[159] The primary outcome of discharge with completely restored valve function, without major complications, was not significantly different between surgery and fibrinolysis groups (71.8% vs 67.5%; OR: 1.22; 95% CI: 0.47-3.19).[159] The primary safety outcome of death, nonfatal stroke, nonfatal major bleed, or systemic embolism at discharge occurred more frequently with surgery compared with fibrinolysis (28.2% vs 7.5%; OR: 5.14; 95% CI: 1.28-20.59), whereas residual valve dysfunction rate at discharge was lower with surgery vs fibrinolysis (0% vs 25%).[159] Anticoagulation is still the primary therapeutic approach for patients with bioprosthetic valve thrombosis.[152,153]

LEFT VENTRICULAR THROMBUS

There is limited high-quality evidence regarding the efficacy and safety of fibrinolytic therapy in the treatment of patients with LV thrombus. Existing data are limited to case reports and case series,[160] with a potential risk of thrombus embolization following fibrinolysis.[161] The 2022 AHA Scientific Statement did not suggest routine fibrinolytic therapy for the primary purpose of LV thrombus treatment.[162] The 2019 AHA/American Stroke Association (ASA) guideline for acute ischemic stroke considered intravenous alteplase reasonable in patients with LV thrombus who have a major acute ischemic stroke that is likely to produce severe disability.[20] Oral anticoagulation remains the standard of care for LV thrombus.[7,160,163,164]

LEFT VENTRICULAR ASSIST DEVICE OCCLUSION

Pump thrombosis is a major adverse event in patients supported by continuous-flow LVADs.[165,166] However, the available evidence on the treatment of LVAD thrombosis is primarily derived from small case series of local or systemic fibrinolysis.[167-169] Professional society guidance documents have provided heterogeneous recommendations regarding the use of fibrinolysis. The 2024 British Societies guideline[36] suggested that in cases of inadequate circulation, immediate temporary mechanical circulatory support or salvage fibrinolytic therapy may be considered. The 2019 EACTS Expert Consensus[37] considered fibrinolysis a potential treatment option for intrapump thrombosis, and pump exchange or urgent transplantation was suggested when feasible. The 2024 International Society for Heart and Lung Transplantation Consensus Statement[170] suggested that fibrinolytic therapy should only be considered in patients with pump thrombosis who fail (or are not candidates for) antithrombotic therapy.

CENTRAL RETINAL ARTERY OCCLUSION

CRAO (also known as “ocular stroke”) is a thromboembolic vascular event affecting the retina, which causes sudden, painless unilateral vision loss, with 80% of patients reaching a final visual acuity of counting fingers or worse with conservative treatment.[171,172] CRAO is clinically distinct from cerebral infarction. There is a lack of proven effective therapies, although fibrinolytic therapy has been explored.

The use of intra-arterial alteplase for CRAO emerged as a potential approach with a lower risk of systemic and intracranial bleeding.[173] One trial investigating intra-arterial alteplase[174] included 82 patients within 20 hours of symptom onset. Clinically significant visual improvement (considered as the logarithm of the minimum angle of resolution ≥0.3) was noted in 60.0% of patients receiving conservative treatment and in 57.1% undergoing local intra-arterial fibrinolysis. The study was stopped prematurely because of futility.

Similar to acute ischemic stroke, the most recent Scientific Statement of the AHA[173] suggested intravenous alteplase for patients with CRAO presenting within 4.5 hours of symptom onset. For patients who are ineligible for intravenous fibrinolysis and present within 6 hours of symptom onset, intra-arterial alteplase may be an option.[174] Several ongoing trials are evaluating the efficacy and safety of fibrinolysis for CRAO (NCT04965038, NCT04526951, and NCT03197194) (Supplemental Table 11).

CEREBRAL VENOUS SINUS THROMBOSIS

Systemic anticoagulation is the first-line treatment for CVST.[175] However, it may be less effective in extensive thrombosis, as approximately 20% of patients with CVST remain disabled or die despite anticoagulation therapy.[175-177] Endovascular fibrinolysis has resulted in almost 90% complete or partial thrombus resolution in patients with CVST.[176] The effectiveness and safety of endovascular treatment (mechanical thrombectomy, local intrasinus fibrinolysis with alteplase or urokinase, or a combination of both) plus anticoagulation vs anticoagulation alone have been tested in the TO-ACT (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis) trial.[178] The trial terminated early because of futility after recruiting 67 of the intended 164 patients with severe CVST.[178] Among 33 patients randomized to endovascular treatment, fibrinolysis was applied to 17.[178] The trial did not show differences in excellent functional outcomes at 12 months (67% vs 68%; RR: 0.99; 95% CI: 0.71-1.38) between the 2 arms.[178] At present, endovascular treatment is considered a rescue option for patients with clinical deterioration despite standard anticoagulation.[179] An ongoing trial (NCT06583889) will evaluate the effectiveness and safety of endovascular treatment vs anticoagulation in 224 patients with CVST and intracranial hypertension.

AGE, SEX, AND RACIAL REPRESENTATION IN FIBRINOLYTIC THERAPY CLINICAL TRIALS

Several studies have noted the underenrollment of certain populations, such as older adults,[180] women,[181] individuals with multiple comorbidities, and racial and ethnic minorities[180,182] in trials of fibrinolytic therapy for thromboembolic diseases. For instance, women were underenrolled by 4.8 percentage points relative to their representation in the underlying populations in RCTs of intravenous fibrinolysis for stroke, resulting in a participation-toprevalence ratio of 0.91 (95% CI: 0.86-0.87).[132] The barriers of equitable representation are likely diverse and may be mitigated by educational campaigns as well as the inclusion of trialists and patients with diverse backgrounds in the design and execution of future trials. This underrepresentation is concerning since, in addition to limiting the external validity of the trials, it has been mirrored by the underutilization of fibrinolytic therapy in these populations in routine clinical practice.[100,183-186]

INTEGRATED INSIGHTS FOR FIBRINOLYSIS ACROSS THROMBOEMBOLIC DISEASES

Fibrinolytic agents are potent activators of endogenous fibrinolysis. However, their effectiveness may be diminished by the chronicity of thrombi, and their safety is affected by underlying bleeding risk as well as type, dose, route, and duration of administration of the fibrinolytic agent. The clinical decision to use systemic fibrinolytic therapy requires a careful assessment of the risk-to-benefit ratio, which is influenced by disease acuity, severity, patient-specific bleeding risk, and the availability of alternative treatment options. In high cardiovascular-risk scenarios, such as PE with hemodynamic instability (and no other strong available option) or acute ischemic stroke with disabling neurologic deficits, fibrinolysis offers a clear therapeutic benefit that often outweighs the bleeding risk to reduce mortality and irreversible organ damage. In STEMI, however, primary PCI is preferred over fibrinolysis when timely access is available because of its superior efficacy and safety. In contrast, in cases such as minor, nondisabling ischemic stroke or low-risk PE, the absolute benefit of fibrinolysis is limited, whereas the risk of major bleeding, particularly intracranial hemorrhage, remains noticeable. Therefore, systemic fibrinolysis is generally not endorsed in these patient populations.

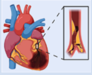
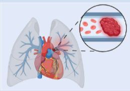
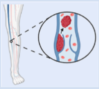
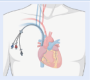
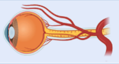
Patients with intermediate cardiovascular risk, such as those with intermediate-risk PE, represent a nuanced clinical population. The PEITHO trial showed that in this group, systemic fibrinolysis significantly reduced the risk of death or hemodynamic decompensation compared with placebo, although at the cost of higher incidences of major bleeding and intracranial bleeding.[75] The balance of efficacy and safety observed in intermediate-risk PE is in some respects comparable with that seen in high-risk conditions. For instance, the NINDS trials demonstrated that systemic fibrinolysis, administered within 3 hours of acute ischemic stroke onset (as a population at high risk of death and disability), significantly improved favorable neurologic outcomes compared with placebo but was associated with an increased risk of symptomatic intracerebral hemorrhage.[1,8] Despite comparable efficacy and bleeding risks in both conditions, regulatory authorities and professional society guidelines have not endorsed routine use of systemic fibrinolysis in intermediate-risk PE,[1,8,72,73] although it is recommended for eligible patients with acute ischemic stroke.[1,19,20] This variation may be partly explained by the higher absolute risk of death or long-term disability in acute ischemic stroke, the time-sensitive nature of neurologic recovery, and the availability of alternative treatment options such as catheter-directed therapies or advanced supportive care for PE. These risk-to-benefit assessments may be revisited if safer regimens or types of agents that activate endogenous fibrinolysis effectively become available.

KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Despite advancements in fibrinolytic therapy, several knowledge gaps warrant further investigation[187] (**Figure 6**). Novel pharmacologic strategies are being studied to enhance endogenous fibrinolysis, with a potential for a better safety profile because of activation of fibrin-bound plasmin. For instance, monoclonal antibodies targeting alpha-2 antiplasmin are currently under investigation in the phase 2 NAIL-IT (Novel alpha-2 Antiplasmin Inactivation for Lysis of Intravascular Thrombi; NCT05408546) trial for intermediate-risk PE, the SIRIUS (Epidemiologic Study of Risk Factors for Deep Vein Thrombosis in Medical Outpatients; NCT06149520) trial for proximal DVT, and the SISTER (Strategy for Improving Stroke Treatment Response; NCT05948566) trial for acute ischemic stroke presenting within 4.5 to 24 hours after onset of symptoms. In addition, inhibitors of thrombin-activatable fibrinolysis inhibitor (TAFI),[188] plasminogen activator inhibitor (PAI)-1,[189] or agents combining both mechanisms[190] have demonstrated potential in preclinical models and merit further exploration in clinical settings.[191] Innovative drug delivery systems, particularly nanocarrier-based platforms, represent another promising avenue.[192] These systems offer targeted delivery of fibrinolytic agents, potentially improving therapeutic efficacy while minimizing systemic bleeding risks. Such technologies may facilitate sustained drug release, enhance stability, and optimize biodistribution.[192]

In cases of severe, life-threatening bleeding following fibrinolytic therapy, cryoprecipitate or

FIGURE 6 Summary of Established Evidence and Future Perspectives for Fibrinolytic Therapy in Thromboembolic Diseases

Indications	Established Evidence	Future Areas of Research
 **STEMI**	Systemic fibrinolysis for patients who cannot undergo primary PCI within 120 min of the first medical contact	Intra-arterial fibrinolysis as an adjunct therapy to PCI for patients with high thrombus burden
 **PE**	Systemic fibrinolysis for patients with high-risk PE	Catheter-directed fibrinolysis or low-dose systemic fibrinolysis for intermediate-high-risk PE
 **DVT**	No established indication for fibrinolysis (may be used in patients with severe symptoms)	Identifying patients who would benefit from catheter-directed fibrinolysis with or without mechanical thrombectomy
Ischemic Stroke	Alteplase and tenecteplase for patients with disabling ischemic stroke within 4.5 hours of symptom onset and imaging-based fibrinolysis beyond 4.5 hours	• Intra-arterial or intravenous fibrinolysis as adjunctive therapy to endovascular thrombectomy • Fibrinolysis with different agents in extended time window
Acute Limb Ischemia	Catheter-directed fibrinolysis with alteplase or urokinase in patients with salvageable limb ischemia	Investigating the use of catheter-directed recombinant staphylokinase
 **CVAD Occlusion**	Low-dose intra-luminal alteplase	Identifying risk factors of embolization after fibrinolysis
Mechanical Prosthetic Valve Thrombosis	Ultraslow low-dose alteplase regimen in patients with obstructive mechanical prosthetic valve thrombosis	Comparing ultraslow low-dose alteplase regimen with surgery
 **Central Retinal Artery Occlusion**	No established indication for fibrinolysis (intravenous alteplase may be used)	Investigating the use of intravenous and intra-arterial fibrinolysis

In addition to the mentioned indications, there is limited evidence for the use of fibrinolysis for patients with left ventricular thrombus, cerebral venous sinus thrombosis, and left ventricular assist device occlusion. Abbreviations as in Figure 1.

fibrinogen concentrate can be administered to correct hypofibrinogenemia, and antifibrinolytic agents, including tranexamic acid or aminocaproic acid, can be used to inhibit ongoing fibrinolysis.[20] Recently, several investigational agents targeting key components of the fibrinolytic system, such as recombinant alpha-2 antiplasmin[193] and monoclonal antibodies modulating plasmin activity,[194,195] have been developed to more specifically suppress fibrinolysis. Further studies are needed to evaluate the clinical effectiveness and safety of these agents.

CONCLUSIONS

Fibrinolytic therapy remains a major management option for thromboembolic diseases. Advances in catheter-directed techniques, dosing strategies, and novel agents may expand therapeutic options and improve the safety of fibrinolytic therapy. Future efforts should focus on identifying subgroups of patients with thromboembolic diseases who benefit the most from fibrinolytic therapy to improve outcomes.

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KEY WORDS fibrinolytic agents, thromboembolism, thrombolytic therapy, thrombosis

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APPENDIX For supplemental tables and figures, please see the online version of this paper.

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